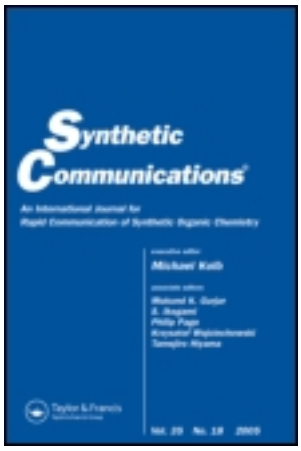


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-one Catalyzed by $Zn(NH_2SO_3)_2$

Min Zhang [a] & Yi-Qun Li [a]

[a] Department of Chemistry, Jinan University, Guangzhou, China

Version of record first published: 16 Aug 2006.

To cite this article: Min Zhang & Yi-Qun Li (2006): Facile One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-one Catalyzed by $Zn(NH_2SO_3)_2$, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:7, 835-841

To link to this article: http://dx.doi.org/10.1080/00397910500464228

Synthetic Communications®, 36: 835–841, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500464228

Facile One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-one Catalyzed by $Zn(NH_2SO_3)_2$

Min Zhang and Yi-Qun Li
Department of Chemistry, Jinan University, Guangzhou, China

Abstract: An efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMS) from aromatic aldehydes, β-keto ester, and urea (or thiourea) in refluxing ethanol using zinc sulfamate as a catalyst is first described here. Compared to the classical Biginelli reaction, this new method consistently has the advantages of good yields (76–96%), short reaction time (2–5 h), no corrosion of equipment, ease of manipulation, and low-cost catalyst.

Keywords: Biginelli reaction, catalyst, zinc sulfamate

Recently, there has been renewed interest in the three-component cyclocondensation of ethyl acetoacetate with aromatic aldehydes and urea (or thiourea) discovered by Biginelli in 1893.[1] 3,4-Dihydropyrimidin-2(1H)-ones (DHPMS) and their derivatives in particular are of pharmacological importantance because of their promising biological effects, including antiviral, antibacterial, antitumor, and antiinflammatory activities.[2] Recently some of them were found to be calcium channel blocks, antihypertensive agents, and alpha-la-antagonists.[3] Moreover, several alkaloids recently isolated from marine sources with interesting biological activities also possess the dihydropyrimidinone core; most notable among these are the batzelladine alkaloids, which have been found to be potent HIV-gp-120-CD4 inhibitors.[4] Therefore, the preparation of this heterocyclic core unit has attracted the attention of many organic chemists. The simple and direct method originally reported by Biginelli involves the one-pot condensation

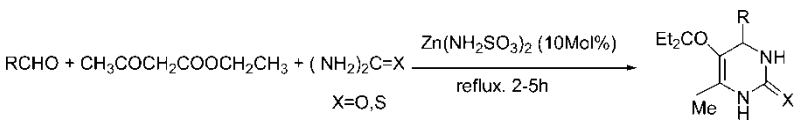
Received in Japan June 24, 2005
Address correspondence to Yi-Qun Li, Department of Chemistry, Jinan University, Guangzhou 510632, China. E-mail: tlyq@jnu.edu.cn

of a β-keto ester with an aldehyde and urea under strongly acidic conditions, but the reaction suffered from drawbacks such as low yields, long reaction time, and strong corrosion of equipment, which has led to the disclosure of several improved procedures using Lewis acids such as $BF_3 \cdot Et_2O$,[5] $LaCl_3$,[6] $Cu(OTf)_2$,[7] $InBr_3$,[8] $ZrCl_4$,[9] $CuCl_2$,[10] $Ag_3PW_{12}O_{40}$,[11] $FeCl_3 \cdot 6H_2O$, and Me_3SiCl[12] and protic acids such as NH_2SO_3H,[13] NH_4Cl,[14] and $KHSO_4$[15] as additives. Other special methods including ionic liquids,[16] microwave irradiation,[17] trimethylsilyl-triflate,[18] polyaniline-bismoclite complex,[19] L-proline,[20] grindstone chemistry,[21] and I_2,[22] also have been employed for this transformation. However, some of these protocols have not been entirely satisfactory because of such drawbacks as low yields, long reaction time, cumbersome experimental processes, and use of organic solvents or moisture-sensitive and costly catalysts. So, it is necessary to find a new catalyst for this important reaction. We have found that zinc sulfamate can smoothly catalyze the three-component cyclocondensation efficiently with the advantages of rapid reaction rates, high yields, no corrosion of equipment, ease of manipulation, and low-cost catalyst.

Various substituted aromatic aldehydes reacted well with urea (or thiourea) and β-keto ester in the presence of a catalytic amount of $Zn(NH_2SO_3)_2$ in ethanol to gave the corresponding DHPMS in 76–96% yields (Scheme 1, Table 1).

The results are shown in Table 1. In all cases studied, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1H)-ones in good to excellent yields. Most important, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently and gave good to excellent yields. However, *o*-substituted aromatic aldehydes needed relatively long reaction times, but low yields were found because of the influence of steric hindrance (Table 1, entries 11, 12, and 13). Under the same condition, also for thiourea, a slightly longer reaction time was required and lower yields were observed owing to its lower activity (Table 1, entries 14, 15, and 16). In comparison to zinc sulfate as the catalyst, the yields decreased to 62% and the reaction time increased to at least 7h by this procedure (Table 1, entry 2).

In conclusion, we have developed a simple and general method for the synthesis of dihydropyrimidinones using the inexpensive, oxygen- and high-temperature-tolerant, easily available zinc sulfamate as the catalyst. The method offers several advantages including high yields, short reaction time,



Scheme 1.

Table 1. Facile one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones[a] catalyzed by $Zn(NH_2SO_3)_2$

Entry	R	X	Time (h)	Yield (%)[b]	Mp (°C)[ref.] Found	Mp (°C)[ref.] Reported
1	C_6H_5	O	3	96	203–205	202–204[13]
2	4-ClC_6H_4	O	3	96 (62[c])	212–214	212–214[13]
3	4-HOC_6H_4	O	3	95	226–228	226–228[13]
4	4-$NO_2C_6H_4$	O	4	96	209–211	208–210[13]
5	4-$CH_3C_6H_4$	O	2	96	170–172	169–171[9]
6	4-$NMe_2C_6H_4$	O	3	92	231–233	229–232[9]
7	4-$CH_3OC_6H_4$	O	3	91	201–203	200–202[13]
8	4-BrC_6H_4	O	4	92	205–208	202–206[23]
9	3-$NO_2C_6H_4$	O	4	82	226–228	225–227[13]
10	4-HO-3-$CH_3OC_6H_3$	O	3	80	231–233	232–233[13]
11	2-ClC_6H_4	O	5	86	216–218	216–218[14]
12	2,4-$2ClC_6H_3$	O	3	88	249–251	251–252[13]
13	2-HOC_6H_4	O	5	76	201–203	199–201[13]
14	C_6H_5	S	5	79	191–193	190–192[9]
15	4-$CH_3OC_6H_4$	S	5	76	150–153	150–152[17]
16	4-HOC_6H_4	S	5	76	191–193	193–194[9]

[a]The products were known and characterized by comparison of their physical and spectral data with those of authentic samples.

[b]Isolated yields of corresponding DHPMS.

[c]Isolated yield with $ZnSO_4$ as the catalyst after 7 h.

and a simple experimental workup procedure, which makes it a useful process for the synthesis of dihydropyrimidinones.

EXPERIMENTAL

Melting points were measured by X6 micro-melting-point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellets on a Bruker Equinox 66 spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 300 (300-MHz) instrument. Benzaldehyde was purified by distillation. Other chemicals were of commercial grade and used without further purification.

General Procedure for Experiment

A mixture of aromatic aldehyde (5 mmol), ethylacetoacetate (5 mmol), urea or thiourea (7.5 mmol), ethanol (12 ml), and $Zn(NH_2SO_3)_2$ (0.1 mmol) was heated and stirred in a round flask for 2–5 h (78°C). TLC indicated the completion of reaction. The mixture was cooled to room temperature, then poured into ice-cold water. The solid was filtered and washed with ice-cold water and purified further by recrystallization (hot ethanol). All the yields mentioned in Table 1 are based on isolated products.

All the compounds were known and characterized by their spectral (IR, ^{1}H NMR) and physical data. Wherever literature examples were available, the data were compared and were found to be identical with authentic samples.

Spectral Data

Ethyl 6-methyl-2-oxo-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 2. Mp 212–214°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.13 (s, 1H, NH), 7.52 (s, 1H, NH), 7.37 (d, $J = 8.4$, 2H, Ar), 7.23 (d, $J = 8.4$, 2H, Ar), 5.62 (d, $J = 3.2$ Hz, 1H, CH), 3.97 (q, $J = 7.1$ Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.08 (t, $J = 7.1$ Hz, 3H, CH_3). IR (KBr) $\nu = 3429$, 3236, 3112, 2975, 1701, 1645 cm^{-1}.

Ethyl 6-methyl-2-oxo-4-(4-hydroxyphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 3. Mp 226–228°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.33 (s, 1H, OH), 9.12 (s, 1H, NH), 7.63 (s, H, NH), 7.05 (d, $J = 8.4$ Hz, 2H, Ar), 7.01 (d, $J = 8.4$ Hz, 2H, Ar), 5.05 (d, $J = 2.86$, 1H, CH), 3.97 (q, $J = 7.09$ Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 1.08 (t, $J = 7.08$ Hz, 3H, CH_3). IR (KBr) $\nu = 3374$, 3280, 3131, 2981, 1687, 1649, 1514 cm^{-1}.

Ethyl 6-methyl-2-oxo-4-(4-methylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 5. Mp 170–172°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.18 (s, 1H, NH), 7.71 (s, H, NH), 7.13 (d, $J = 8.5$ Hz, 2H, Ar), 6.69 (d, $J = 8.5$ Hz, 2H, Ar), 5.12 (d, $J = 3.28$, 1H, CH), 3.98 (q, $J = 7.05$ Hz, 2H, CH_2), 3.36 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.10 (t, $J = 7.1$ Hz, 3H, CH_3). IR (KBr) $\nu = 3417$, 3241, 3120, 2984, 1687, 1649, 1512 cm^{-1}.

Ethyl 6-methyl-2-oxo-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 7. Mp 201–203°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.17 (s, 1H, NH), 7.67 (s, H, NH), 7.15 (d, $J = 7.8$ Hz, 2H, Ar), 6.88 (d, $J = 7.8$ Hz, 2H, Ar), 5.12 (d, $J = 2.9$ Hz, 1H, CH), 3.98 (q, $J = 6.61$ Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3), 1.09 (t, $J = 6.69$ Hz, 3H, CH_3). IR (KBr) $\nu = 3355$, 3231, 3108, 2973, 1700, 1645, 1456 cm^{-1}.

Ethyl 6-methyl-2-oxo-4-(4-bromophenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 8. Mp 205–208°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.23 (s, 1H, NH), 7.79 (s, H, NH), 7.53 (d, $J = 8.40$ Hz, 2H, Ar), 7.19 (d, $J = 8.41$ Hz, 2H, Ar), 5.12 (d, $J = 3.15$, 1H, CH), 3.97 (q, $J = 7.08$ Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.09 (t, $J = 7.1$ Hz, 3H, CH_3). IR (KBr) $\nu = 3429$, 3260, 3130, 2980, 1700, 1647, 1458 cm^{-1}.

Ethyl 6-methyl-2-oxo-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate 11. Mp 216–218°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.30 (s, 1H, NH), 7.72 (s, 1H, NH), 7.20–7.46 (m, 4H, Ar), 5.63 (d, $J = 2.68$, 1H, CH), 3.91 (q, $J = 7.05$ Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.08 (t, $J = 7.1$ Hz, 3H, CH_3). IR (KBr) $\nu = 3353$, 3235, 3117, 2978, 1697, 1644 cm^{-1}.

ACKNOWLEDGMENTS

The project was supported by the National Natural Science Foundation of China (No. 20272018) and the Guangdong Natural Science Foundation (Nos. 021166, 04010458).

REFERENCES

1. Biginelli, P. Aldehyde-urea derivatives of aceto- and oxaloacetic acids. *Gazz. Chim. Ital.* **1893**, *23*, 360.
2. Kappe, C. O. 100 years of Biginelli dihydropyrimidine synthesis. *Tetrahedron* **1993**, *49*, 6937.
3. Kappe, C. O. Biologically active dihydropyrimidones of the Biginelli type—A literature survey. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

4. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Browse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. Novel alkaloids from the sponge *Batzella* SP: Inhibitors of HIV gpl2O-human CD4 binding. *J. Org. Chem.* **1995**, *60*, 1182.
5. Hu, E. H.; Sidler, D. R.; Dolling, U. H. Unprecedented catalytic three-component one-pot condensation reaction: An efficient synthesis of 5-alkoxy-carbonyl-4-aryl-3,4-dihydrpyrimidin-2(1H)-ones. *J. Org. Chem.* **1998**, *63*, 3454.
6. Lu, J.; Wang, Z.; Yang, B.; Ma, H. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using lanthanum chloride as a catalyst. *Tetrahedron Lett.* **2000**, *41*, 9075.
7. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. $Cu(OTf)_2$: A reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett.* **2003**, *44*, 3305.
8. Martins, M. A. P.; Teixeira, M. V. M.; Cunico, V.; Scapin, E.; Mayer, R.; Pereira, M. P.; Zanatta, N.; Bonacorso, H. G.; Peppe, C.; Yuan, Y. F. Indium(III) bromide–catalyzed one-pot synthesis of trichloromethylated tetrahydropyrimidinones. *Tetrahedron Lett.* **2004**, *45*, 8991–8994.
9. Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. Zirconium(IV) chloride–catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett.* **2002**, *43*, 2657–2659.
10. Manjula, A.; Rao, B. V.; Neelakantan, P. An inexpensive protocol for Biginelli reaction. *Synth. Commun.* **2004**, *34* (14), 2665–2671.
11. Yadav, J. S.; Reddy, B. V. S.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. Green protocol for the Biginelli three-component reaction: $Ag_3PW_{12}O_{40}$ as a novel, water-tolerant heteropolyacid for the synthesis of 3,4-dihydropyrimidinones. *Eur. J. Org. Chem.* **2004**, *3*, 552–557.
12. Xu, L. W.; Wang, Z. T.; Xia, C. G.; Li, L.; Zhao, P. Q. Improved protocol for the three-component Biginelli reactions and Biginelli-like Mannich reactions of carbamates, aldehydes, and ketones. *Helv. Chim. Acta.* **2004**, *87* (10), 2608–2612.
13. Li, J. T.; Han, J. F.; Yang, J. H.; Li, T. S. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation. *Ultrason. Sonochem.* **2003**, *10*, 119–122.
14. Shaabani, A.; Bazgir, A.; Teimouri, F. Ammonium chloride–catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(H)-ones under solvent-free conditions. *Tetrahedron Lett.* **2003**, *44*, 2757.
15. Tu, S. J.; Fang, F.; Zhu, S. L.; Li, T. J.; Zhang, X. J.; Zhuang, Q. Y. A new Biginelli reaction procedure using potassium hydrogen sulfate as the promoter for an efficient synthesis of 3,4-dihydropyrimidin-2(1H)-one. *Synlett* **2004**, 537–539.
16. Peng, J. J.; Deng, Y. Q. Ionic liquids–catalyzed Biginelli reaction under solvent-free conditions. *Tetrahedron Lett.* **2001**, *42*, 5917–5919.
17. Min, X.; Wang, S. H.; Yuan, W. B. Lewis acid–catalyzed electrophilic substitution of indole with aldehydes and Schiff's base under microwave solvent-free irradiation. *Synth. Commun.* **2004**, *34* (17), 3175–3182.
18. Bose, D. S.; Kumar, R. K.; Fatima, L. A remarkable rate acceleration of the one-pot three-component cyclo-condensation reaction at room temperature: An expedient synthesis of mitotic Kinesin Eg5 inhibitor monastrol. *Synlett* **2004**, 279–282.
19. Gangadasu, B.; Palaniappan, S.; Rao, V. J. One-pot synthesis of dihydropyrimidinones using polyaniline-bismoclite complex. A facile and reusable catalyst for the Biginelli reaction. *Synlett* **2004**, 1285–1287.

20. Yadav, J. S.; Kumar, S. P.; Kondaji, G.; Rao, R. S.; Nagaiah, K. A novel L-proline–catalyzed Biginelli reaction: One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. *Chem. Lett.* **2004**, *33* (9), 1168–1169.
21. Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakrabortyb, G.; Manhasa, M. S. A simplied green chemistry approach to the Biginelli reaction using grindstone chemistry. *Tetradron Lett.* **2004**, *45*, 8351–8353.
22. Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T. Y.; Zubaidhaa, P. K. An efficient, high yield protocol for the one-pot synthesis of dihydropyrimidin-2(1H)-ones catalyzed by iodine. *Tetrahedron Lett.* **2004**, *45*, 9111–9113.
23. Li, Y. X.; Bao, W. L. Microwave-assisted solventless Biginelli reaction catalyzed by montmorillonite clay–$SmCl_3 \cdot 6H_2O$ system. *Chin. Chem. Lett.* **2003**, *14* (10), 993–995.